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TITLE: Is Breast Densitometry a Measure of Breast Cancer Risk?

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<b>13. ABSTRACT (Maximum 200 Words)</b> Perhaps the least recognized risk factor for breast cancer is breast density. Other than age, breast density, as measured using the radiographic contrast in mammograms between fat and nonfatty tissue, has been shown to be one of the strongest indicators of breast cancer risk available. The primary aim of our research is to fully develop new technologies, dual and single energy x-ray absorptiometry (DXA and SXA), for breast densitometry that could be used to clinically assess the risk of breast cancer and to serve as a sensitive and highly reproducible surrogate marker for testing new methods for preventing breast cancer. DXA %FAT was found to be highly correlated to phantom percent glandular density ( $r > 0.998$ ). In addition, DXA %FAT was found to be highly correlated to mammographic density using excised cadaveric breasts ( $r_{\text{adjusted}} = 0.83$ ). DXA precision (SD) on whole breast tissue samples was 0.5% without repositioning and 1.1% with breast repositioning. Based on this validation of the DXA technique, we have constructed an In vivo DXA positioning aid to be used on commercial DXA equipment and in planned clinical validation trials. With regards to SXA, a workstation and a dynamically adjustable phantom have been designed and constructed. However, full validation of precision and accuracy have not been completed. We plan to follow these encouraging initial results with a case-control study to show that compositional breast density is as highly or more highly predictive of cancer risk than mammographic density alone.				
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## Introduction

Perhaps the least recognized risk factor for breast cancer is breast density. Other than age, breast density, as measured using the radiographic contrast in mammograms between fat and nonfatty tissue, has been shown to be one of the strongest indicators of breast cancer risk available. Women who have greater than 50% of total breast area that is "mammographically" dense are at 3 to 5 fold greater risk of breast cancer than women with less than 25% mammographically dense breasts. The primary aim of our research is to fully develop new technologies for breast densitometry that clinically assess the risk of breast cancer and to serve as a sensitive and highly reproducible surrogate marker for testing new methods for preventing breast cancer. Developing the ability to quantify breast density could lead to new risk stratification strategies for screening and treatment of breast cancer, and to increased collaboration between epidemiologists and basic scientists working to better understand how proliferated breast stroma (mammographic breast densities) may interact with breast epithelium to promote the growth of breast tumor cells. The studies we propose are essential pilot studies that we believe will make a strong case for funding of larger studies to establish the value of our new method.

## Body

Our aim is to develop new methods to measure the breast tissue composition on a pixel by pixel basis. Breast tissue can be modeled as being composed of just two materials: fat and glandular tissue. Using this two-component model, the combination of fat and lean mass that produces the x-ray attenuation is calculated for each pixel. Summing all pixels in the mammogram would result in a total fat and glandular mass and could be represented as a percentage glandular density (%GD). This method has many advantages. First, it eliminates the subjective evaluation of dense areas or uncalibrated thresholds. Second, it is a true measure of breast compositional density instead of x-ray opacity. Third, breast compositional breast should be more selective (higher odds ratio for cancer risk) than mammographic density since it uses all the contrast information in its measure. That is, all the image gray scale values contribute to the compositional density. This increases the accuracy, dynamic range and precision of the measurement. This is the principal difference between mammographic density and compositional density.

We are developing two techniques for measuring breast compositional density based on dual (DXA) and single (SXA) x-ray absorptiometry. The advantages of DXA and SXA over MRI and CT are that these examination are already part of the annual clinical procedures women are recommended to undergo. DXA is the most common diagnostic method for osteoporosis. A low-dose breast examination added to the standard hip or spine DXA would add little cost. SXA is a modification of standard mammography using film and well suited for new technologies such as digital mammographic detectors or computed radiographic screens. An SXA breast density examination does not add any additional views nor dose to the mammography examination and is automatically evaluated.

DXA is most commonly used to solve for bone density to diagnose osteoporosis but is also used to quantify in vivo whole body %FAT. By subtracting two x-ray images acquired at different x-ray energies, one component (say soft tissue) of a two component model (say bone and soft tissue) can be eliminated from the subtraction image and leave a bone mass image (when soft tissue is subtracted) or a %FAT image (when the model just include fat and lean tissue is and lean is subtracted). DXA is a highly developed technique with very high precision, approx. 1% C.V. for bone and soft tissue density, and is available on over 10,000 dedicated clinical densitometers around the world. It is low dose in comparison to mammograms since the image can be spatially noisy since tissue mass is typically quantified in large regions of interests. Several investigators have suggested using DXA techniques on mammographic equipment to better identify calcification or improve image contrast (1-5) but to the author's knowledge, no one has actually performed a DXA study of breast density and this technique is not available on standard mammography devices.

The second technique, which is the subject of a pending patent, may have equivalently high precision and accuracy to the DXA technique with several advantages. Like the DXA method, the advantages are that: 1) it is not subjectively measured like mammographic density, 2) It is an accurate representation of breast density versus mammographic opacity, 3) it can be measured from standard mammograms with the inclusion of a novel reference phantom, and 4) it is easily adaptable and optimal for the new solid state digital mammography devices. However, there are several challenges to solve that may limit the accuracy of SXA. First, the method relies in the fact that the object being measured is of a constant thickness. This is true for approximately 75% of the compressed breast area, but the assumption breaks down in the surrounding breast perimeter. Second, the technique relies on a novel reference phantom to be in the field of measure and that it automatically adjusts

to the compression thickness of the breast without interfering with the technologist or patient. In addition, calcifications are more dense (lean) than pure glandular tissue and if not discriminated could increase the glandular density measure above its actual value. These challenges can only be addressed in future clinical studies.

The SXA methodology is described below. The compressed breast is modeled as a uniformly thick tissue mass of two materials, fat and glandular tissue. If a reference of fat and gland-equivalent materials is imaged with the compressed breast (a phantom), and if the reference materials are defined to be the same thickness as the breast, then the image attenuation measurements (the digitized gray scale values) can be converted to percent glandular density, %GD. Mathematically, this is expressed as

$$\%GD = 1 - \frac{\sum_{i,j=0}^{N,M} \frac{\ln(\frac{I_{i,j}}{I'})}{\ln(\frac{I''}{I'})} a_{i,j}}{\sum_{i,j=0}^{N,M} a_{i,j} \left( \frac{\ln(\frac{I_{i,j}}{I'})}{\ln(\frac{I''}{I'})} + \left(1 - \frac{\ln(\frac{I_{i,j}}{I'})}{\ln(\frac{I''}{I'})}\right) \frac{\rho_l}{\rho_f} \right)} * 100$$

where  $I'$  = the transmission through the fat reference,  $I''$  is the transmission through the gland reference,  $I_{i,j}$  = transmission at pixel row  $i$  and column  $j$ ,  $\rho_l$  and  $\rho_f$  are the density of the lean (gland) and fat materials respectively, and  $a_{i,j}$  is the cross sectional area of each pixel.  $M$  and  $N$  are the row and column size of the digitized image. Thus the percent glandular density can be quantified without knowing the absolute compression thickness or the exact x-ray technique. The reference phantom is measured at the exact same time and x-ray conditions as the breast and the two reference points bound the expected gray scale values. Thus, the mammogram can be acquired to maximize contrast for diagnostic work without putting limitation on the x-ray technique and still be useful for SXA. At this time, we have conducted preliminary tests with novel SXA phantoms to know that the method is sound and may be as accurate as DXA.

We report on our study progress by listing the specific aims from our proposal and discussing our progress for each.

### 1. Calibrate and characterize breast densitometry using tissue-equivalent phantoms.

#### A. DXA Methodology

**Methods/Materials:** DXA devices assume a two-component soft-tissue model of fat and muscle when quantifying soft tissue composition. To investigate the validity of using DXA techniques for determining percent breast glandular tissue density (%GD) the M17 phantom (CIRS, Inc., Norfolk, VA) was used as a breast density calibration tool. The M17 is a density step phantom of constant thickness that simulates different ratios of breast glandular tissue and adipose fat. See Figure 1. This phantom is an approximate atomic equivalent to adipose fat and breast glandular tissue as reported by Hammerstein, et al. (6). The phantom's attenuation coefficients are within 1% of their respective fat/gland ratios from 10 to 200 keV. The density ranged from 0 percent glandular density to 100% glandular density in 6 steps. Note that the inner clear acrylic section was not included in our comparison since acrylic is not a stable representation of tissue across a wide x-ray energy range. The M17 phantom was scanned 10 times on the DXA scanner without repositioning. A second M17 phantom was then placed on top of the first to simulate a thicker breast. The %GD, as reported by the phantom manufacturer was compared to the percentage fat (%FAT) reported by DXA.

**Results:** The relationship between true %GD of the phantom and %FAT by DXA was

$$\%GD = -0.627 * \%FAT_{DXA} + 72.5$$

with a  $r^2$  value of 0.998 and a SEE = 1.85 g. See Figure 2 below.

#### B. SXA Methodology

The SXA method is based on a bone densitometry technique called single x-ray absorptiometry (SXA) in which one x-ray image is used to solve for the composition of two materials (7). Our approach is based upon having two reference materials, a fat and glandular tissue reference, of the same thickness as the compressed breast that is imaged with each patient. The two materials we actually use are the approximate atomic and density equivalents to 100% fat and 100% glandular tissue (6). The materials were specifically made for this purpose (CIRS, Inc., Norfolk, VA). The phantom consists of two wedges (right triangles of a uniform thickness), one

small and one large, such that, when held together along their longest edges, they create parallel surfaces on the top and bottom. See Figure 3. When the smaller wedge is attached to the top compression paddle and the lower wedge allowed to slide along the lower compression surface (Bucky grid) while maintaining contact with the smaller wedge (a spring), the two wedges conform to the compression thickness and provide areas of pure fat and gland sample in the mammogram the same thickness as the breast. A conceptual drawing of how the phantom is used is shown in Figure 4. Over its height range, the prototype phantom's projected size (4.3 cm x 9.6 cm) allows for a generous 1 sq. inch sample of each reference entirely through the phantom's full thickness. At the moment, the phantom footprint is large but in a review of 377 randomly selected 8" x 10" CC mammograms, the phantom could have been placed in the opposite corners from the film tag and only have overlapped the breast image on 4 films.

The development of the SXA software has been slower than anticipated. Table 1 outlines the software development and where we stand in the development.

**Table 1: SXA development progress**

Task	Completed
1. Create SXA algorithm in Medx software	Done
2. Write Import tool for mammograms	Done
3. Create Flat field algorithm to create uniform gray-scale field.	Partially Done
4. Create algorithm to select uniform thickness portion of breast	Done
5. Integrate the algorithm from 4. Into workstation	Not Done
6. Develop robust digitizing technique for mammograms	Not Done
7. Validate the SXA method using density step wedge phantom	Not Done
8. Compare precision and accuracy of SXA to standard mammographic density	Not Done

Figure 5 is a screen capture image of the SXA workstation as it is now. The image is of a cadaver breast. The image was generated before correcting for the x-ray field nonuniformities. In summary, we did not completely validate the SXA image in this year study period. We are seeking additional funds to finish this part of the project.

*2. DXA scans and mammograms of breast pairs will be measured to determine if left/right differences exist.*

This aim was to be carried out using the cadaver breasts. Collecting cadaver breast was very difficult. Although we had assurances from the Anatomy Department we could expect approximately 20 pair of breast in the 1 year study period, we only received 5 pair (10 breasts). The first 4 pair were analyzed completely. The last pair has yet to be analyzed and is in frozen storage. 1 pair of the four breast came back with hepatitis positive test such that we could not complete some of the examinations.

Methods: 3 pairs of breast were compared for left right differences in the DXA measurements. The significance of the difference was determined using a paired t-test to calculate a Pearson's p-value.

Results: The results are summarized in Table 2 below. None of the measures were shown to be statistically significantly different with a p-value less than 0.05. However, it is difficult to generalize since there were only three paired comparisons.



**Table 2: Statistical significance of the difference between left and right breasts. This test was severely limited by the small number of samples.**

Measure	p-value
Total Mass (g)	0.17
Total Fat (g)	0.05
Total Lean (g)	0.84
Percent Fat (%)	0.64
Percent Glandular Density (%)	0.64

3. *A subset of breasts will be radiographed several times and DXA scanned several times with repositioning of the breast to quantify precision of the mammographic and DXA density measures.*

These results are summarized in Appendix 1.

4. *Finally, we will compare the new breast densitometry method to conventional mammographic density. The DXA densities will be correlated to the mammographic density as well as the density scores. DXA Percent Breast Fat thresholds will be defined to correspond to the scoring classification and to percentage mammographic densities.*

These results are summarized in Appendix 1.

#### 5. *Additional Studies:*

The purpose of the trial was to validate if DXA and SXA are valid densitometry methods for measuring breast composition. As seen in Appendix 1, we did validate the DXA method. The SXA method is still under development. In addition, to now use DXA in clinical trials, we also performed the work.

#### A. *DXA Positioning Aid for in vitro studies*

As part of a previous effort funded by the Department of Defense, we have designed and constructed a positioning aid for the in vivo measurement of breast compositional density. The positioning aid is made of acrylic and rests on top of the DXA scanner's tabletop. It allows for one breast to protrude through the positioner and hang in the x-ray path. This is shown in schematic in Figure 6. A subject being positioned on the Hologic device and positioning aid is shown in Figure 7. The entire breast is imaged in the prone pendulous view without compression.

## Key Research Accomplishments

1. DXA %FAT was found to be highly correlated to phantom percent glandular density ( $r > 0.998$ ).
2. DXA %FAT was found to be highly correlated to mammographic density using excised cadaveric breasts ( $r_{\text{adjusted}} = 0.83$ ).
3. DXA precision (SD) on whole breast tissue samples was 0.5% without repositioning.
4. DXA precision (SD) on whole breast tissue samples was 1.1% with breast repositioning.
5. In vivo DXA positioning aid has been designed to be used on commercial DXA equipment.

## Reportable Outcomes

### *Publications*

1. **Shepherd, J.A.**, K. K. Kerlikowske, R. Smith-Bindman, H.K. Genant, and S.R. Cummings. Can Dual X-ray Absorptiometry Accurately and Precisely Measure Breast Density? Accepted and to be publication in *Radiology*, April, 2001.

### *Conference Presentations*

2. **Shepherd, J.A.**, Kerlikowske, K., Genant, H.K., Cummings, S.R. Can Dual X-ray Absorptiometry Accurately and Precisely Measure Breast Density to Quantify Cancer Risk? Presented at the UCSF Breast Oncology Program Retreat, February 9<sup>th</sup>, 2001.
3. Swarnakar, S., S. Prevrhal, K. Kerlikowske, S. Cummings, H.K. Genant, and **J.A. Shepherd**. A Mammographic Density Reading Service for Clinical Drug Trials. InfoRAD presentation at the Annual Meeting of the Radiological Society of North America (RSNA), November 28<sup>th</sup>, 2000, Chicago, IL.
4. **Shepherd, J.A.**, Prevrhal S., Genant, H.K., A New Method for Monitoring Osteolysis using Dual X-Ray Absorptiometry Difference Imaging. To be orally presented (Shepherd) at the Annual Meeting of the Radiological Society of North America (RSNA), November 28<sup>th</sup>, 2000, Chicago, IL.

### *Patent Submissions*

FILED 5/11/01 (date filed) A Device and Method for Determining Proportions of Body Materials

### *Funding Applied for Based on this Work*

Period:	01/01/02 – 12/31/02
Source:	The American Cancer Society
Title:	A Prospective Measure of Cancer Risk and Breast Density
Role:	Principal Investigator
Annualized Support:	15 %
Total Requested	
Funding:	\$466,740
Desc:	This study was to continue the development of the SXA methodology as well as measure actual cancer risk factors associated with the DXA and SXA measurement.
Status:	Submitted 04/01/01. Not funded. Proposal in revision for resubmission.

## Conclusions

The conclusion to the study is that we have shown that commercial DXA devices can be used to measure breast compositional density. Furthermore, although we did not meet our goal to have a validated workstation for the SXA method, we have demonstrated that the workstation is in progress and is near completion such that validation may proceed soon.

The impact of compositional density has yet to be seen. Now that we know we can measure compositional density with high precision and accuracy, it must be shown that compositional density is as good or better risk factor that mammographic density. We are now initiating a clinical prospective pilot study to compare DXA, SXA, and Mammographic Density on women with recently diagnosed cancer versus non-cancer controls.

### ***The So What Test?***

Research on breast cancer is severely handicapped by the lack of a reliable marker of the effect of promising drugs for prevention of cancer. Trials to test new drugs to reduce cancer risk require on the order of 10,000 high risk women studied for 4 or 5 years at a cost of well over \$30 million. Markers of change in risk, such as decrease in breast density, are gaining interest and widespread use in clinical trials with an aim to substantially decrease the size, duration and cost of early-stage trials to test new drugs (8, 9).

Thus, we believe that a measurement of breast compositional density (DXA or SXA) that is integrated into routine mammography or densitometry will have several important roles in clinical practice and clinical research:

1. To give women and doctors an estimate of breast cancer risks.
2. To identify women who will benefit most by available (and coming) treatments to prevent breast cancer.
3. To monitor preventive treatments and behavioral changes.
4. To determine whether these treatments reduce breast density and the associated risk of breast cancer.
5. To enable pharmaceutical companies and researchers to test the potential value of promising new drugs for reducing risk of breast cancer before committing to hugely expensive Phase III and Phase IV trials.

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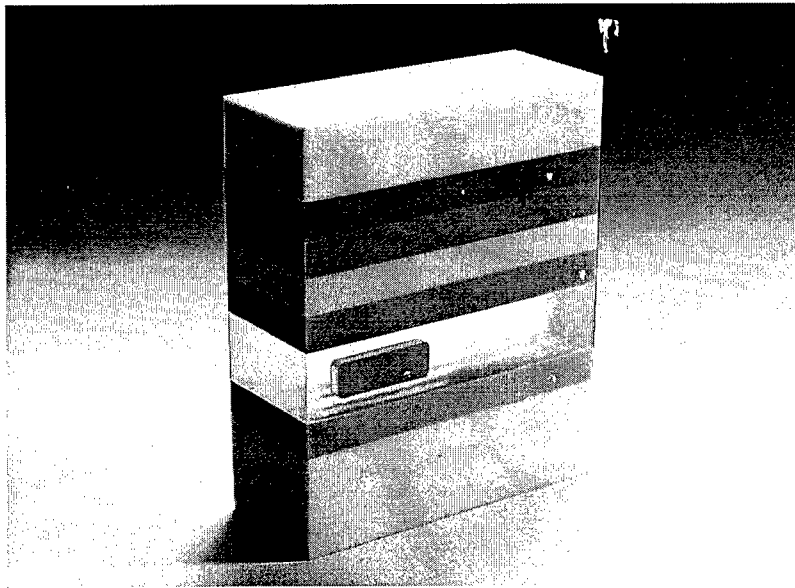


Figure 1: Model 17 phantom by CIRS, Inc. Phantom is made of constant thickness steps of varying thickness from 100% fat (0% glandular tissue) to 0% fat (100 % glandular tissue). Acrylic mid step is ignored since it is not a stable tissue equivalence over both the SXA and DXA energy range.

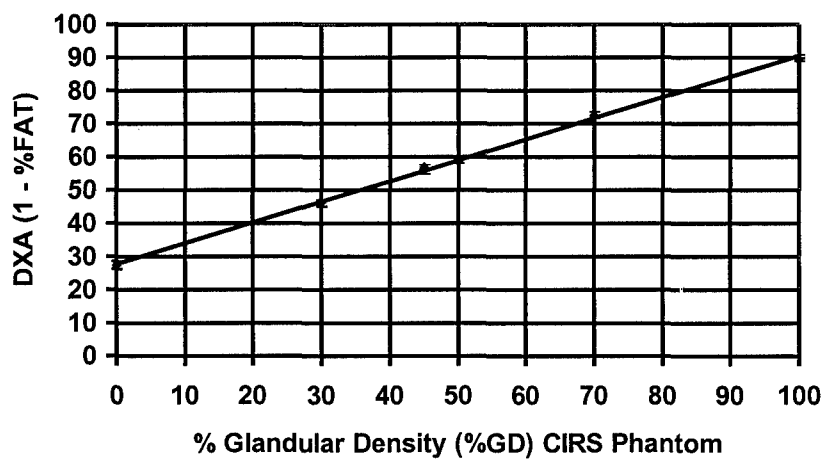


Figure 2: Calibration of %FAT DXA to % Glandular Density using M17 phantom

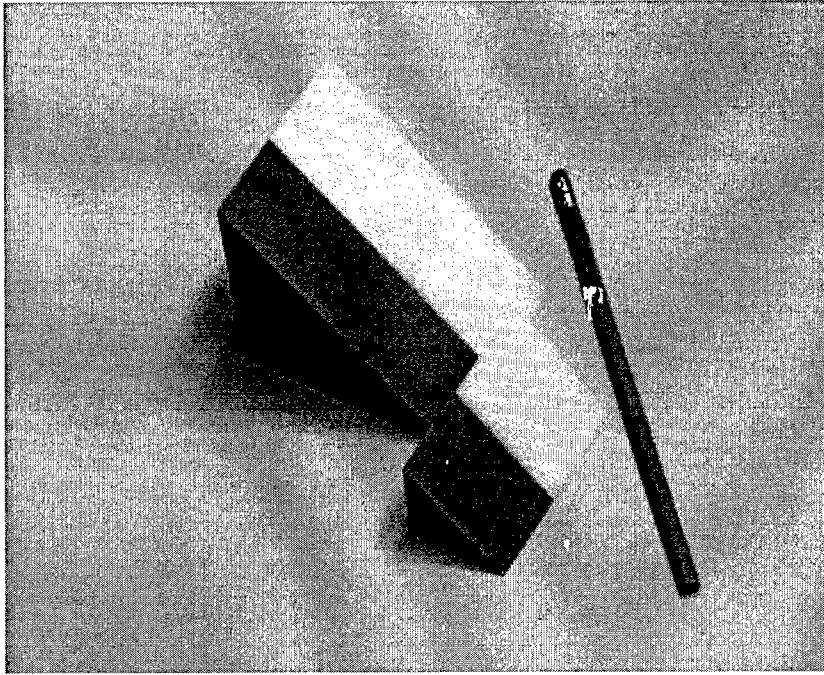


Figure 3: Two separated pieces of dual wedge SXA phantom. Each wedge is made of two materials: 100% fat equivalent, and 100% glandular equivalent. The wedges joined together to form the SXA compressible phantom.

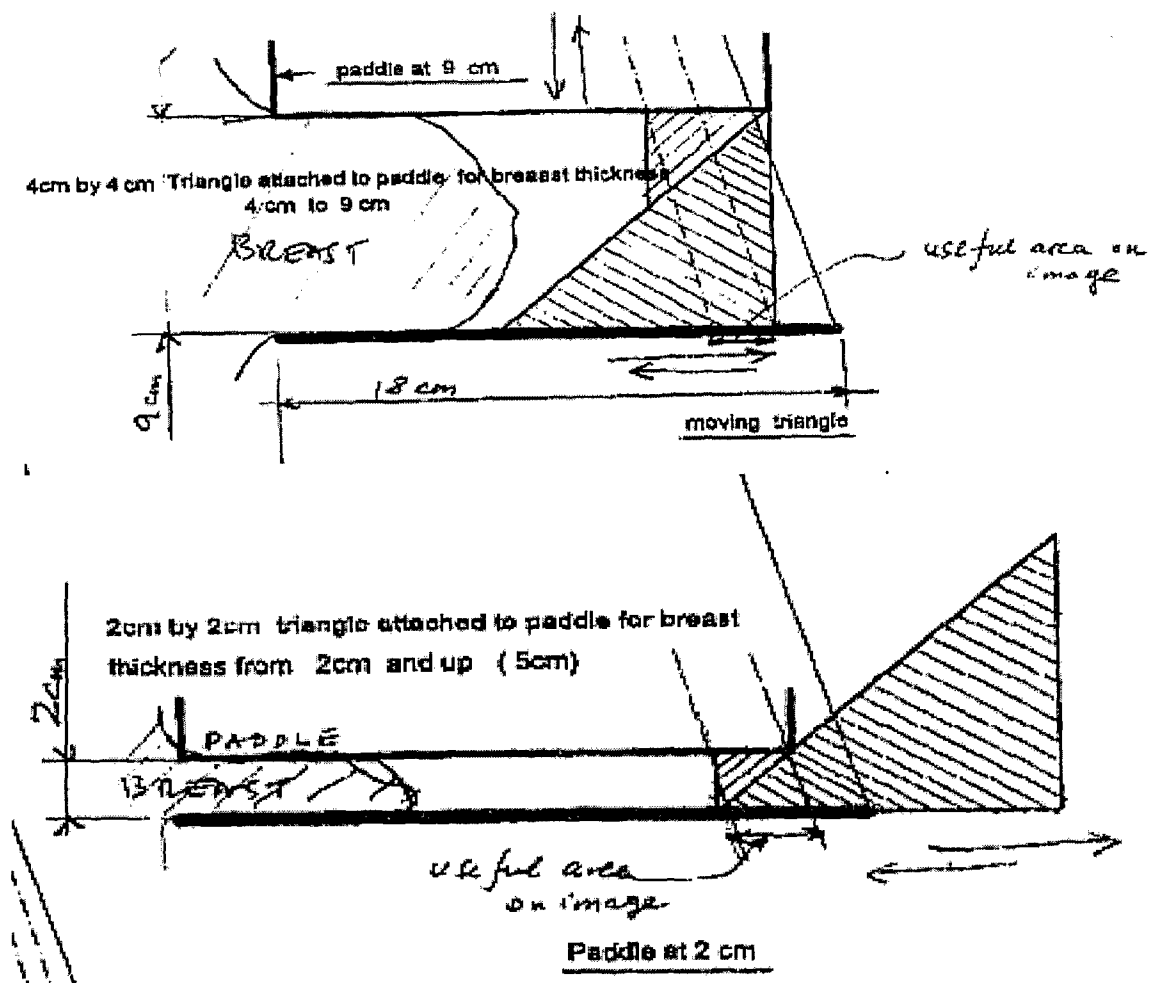


Figure 4: Concept drawing of the dual wedge SXA phantom positioned for a thick (top) and thin (bottom) breast. In both cases, the phantom creates reference areas of fat and gland at the same thickness as the compressed breast.

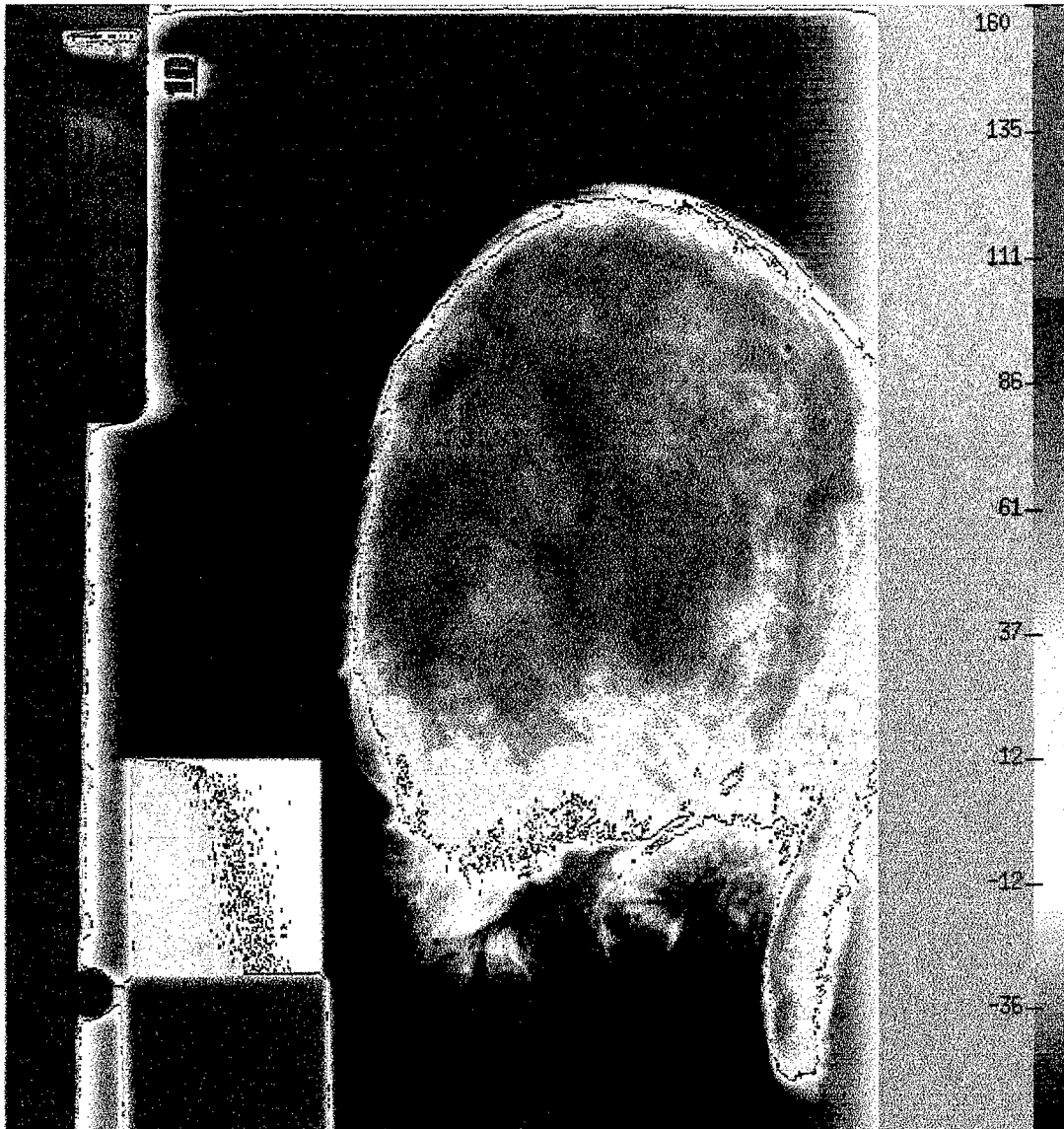


Figure 5: SXA analyzed image of a cadaver breast. The yellow tissue is pure adipose fat while the red is lean tissue. Green is super lean (over 100% glandular tissue) which would highlight calcifications. The gray scale part of the image is super fat. Parts of the breast tissue that are less thick than the phantom (peripheral edge for in vivo scans) will be in the super fat region.



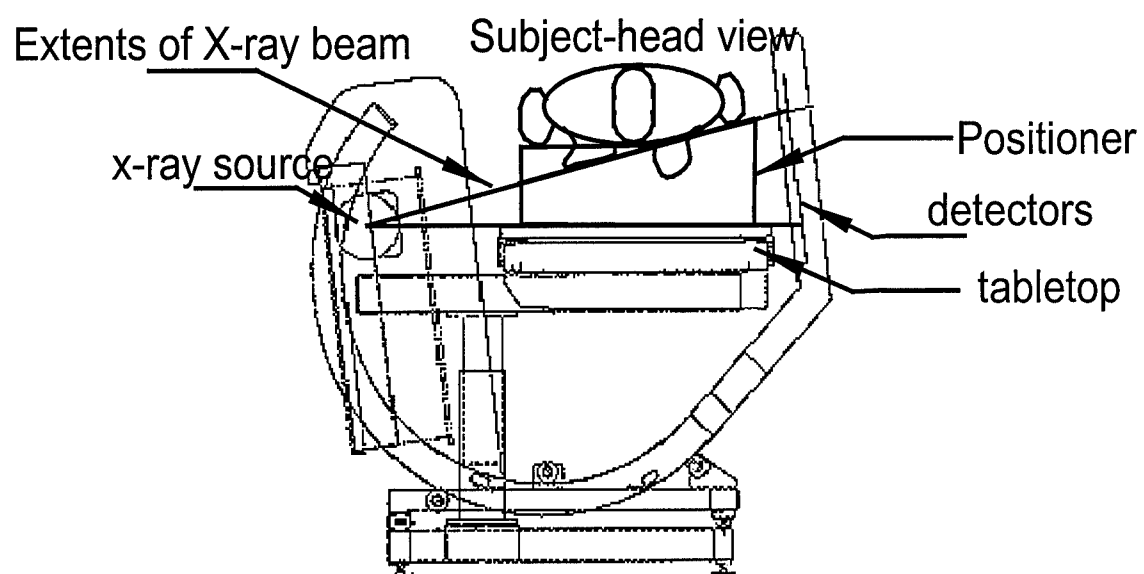


Figure 6: Schematic of a patient positioned for a DXA breast compositional density scan. The densitometer is shown in cross section with its x-ray gantry in the lateral position.



Figure 7: Volunteer positioned on top of the DXA breast positioner.



## **Title: Dual X-ray Absorptiometry Measurement of Breast Density—Feasibility**

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## DXA Breast Density

**Abstract (60 word)**

We report on the ability of Dual Energy Absorptiometry (DXA) to quantify breast density using a variable breast composition phantom and excised cadaver breasts. DXA %FAT was found to be highly correlated to phantom percent glandular density ( $r > 0.998$ ) and to mammographic density ( $r_{\text{adjusted}} = 0.83$ ). DXA precision (SD) was 0.5% and 1.1% without and with breast repositioning. We conclude that commercial DXA devices can be used to accurately and precisely estimate breast tissue density.

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**Introduction**

Perhaps the least recognized risk factor for breast cancer risk is breast density. Other than age, breast density has been shown to be one of the strongest indicators of breast cancer risk. Women who have greater than 50% of total breast area that is mammographically dense are at 3 to 5 fold greater risk of breast cancer than women with less than 25% mammographically dense breasts (1-4). Recently, breast density has been linked to specific biological processes in the breast that give rise to histological features (5), such as atypical hyperplasia and carcinoma in situ, known to be related to increased breast cancer risk. For these reasons, breast density may be an important measure to monitor in clinical drug trials and epidemiological cancer risk studies.

Breast density was initially described using a semi-quantitative classification system that categorized breast density into one of four categories by taking into account the quantitative (amount of density) and qualitative nature of the density (diffuse or pronounced ductal structures, dense parenchymal patterns) (3,4,6,7).

A more quantitative approach is to measure the area of mammographically dense breast relative to the total projected breast area. In this paper, we will refer to this as mammographic density (3,8,9). Mammographic density is a quantitative continuous grading from 0 to 100% measured by delineating the radiographically dense areas on the mammogram from the entire breast area and providing a percentage breast density (PD) defined as (10)

$$PD = \frac{(\text{high radiographic density area})}{(\text{total breast area})} * 100$$

Equation 1.

Although quantitative, this method is limited by the fact that films are calibrated for optical density not mass density, and a unique threshold of breast density is selected by a reader for each image. In addition, the total and dense projected areas will change based on the amount of breast

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compression. The reproducibility (CV) of delineating dense regions combined with patient repositioning errors is generally found to be approximately 5% or more (11). Tamoxifen, a cancer risk reducing therapy, has been shown to decrease breast density by 4.3% per year in cancer cases (12). Thus, the sensitivity of PD to predict risk of breast cancer or to detect response to therapy may be similar to that of categorical methods and insufficient to monitor therapeutic changes in breast density for individuals.

There are compelling reasons to use Dual X-ray Absorptiometry (DXA) techniques to measure breast composition: 1) DXA is the gold standard for measuring whole body composition because of its low radiation dose and high accuracy and precision (13), 2) the precision and accuracy of DXA have been characterized in small animals less than 600g (14), similar to the size of a human breast, 3) the technique does not require a subjective interpretation of results, 4) breast compression is not required and 5) the technique is readily available across the world for measuring bone density and diagnosing osteoporosis. Our specific goals for this study were to calibrate a commercially available DXA device to measure breast glandular density, quantify in vitro precision using cadaver breasts, and compare our measurements to conventional mammographic density.

### Materials and Methods

**Devices:** The DXA densitometer used was the Hologic QDR-4500A (Hologic, Inc., Bedford, MA). The software version was V9.10 and scans were acquired with the Small Animal/Rat Whole Body scan protocol. The scan area was  $18 \times 36 \text{ cm}^2$  with a pixel size of 1 mm x 1.5 mm. The scanner acquired a low and high energy image at 100 kVp and 140 kVp respectively. The entrance dose was 30 mR. Values from the densitometer were recorded as %FAT, Total Fat,

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Total Lean, and Total Mass. The scan objects were placed on the table and scanned with the x-ray gantry in the standard vertical position.

Phantom Measurements: The M17 phantom (CIRS, Inc., Norfolk, VA) was used as a breast density calibration tool. The M17 is a density step phantom of constant thickness that simulates different ratios of breast glandular tissue and adipose fat (Figure 1). This phantom is an approximate atomic equivalent to adipose fat and breast glandular tissue as reported by Hammerstein, et al. (15). The phantom's attenuation coefficients are within 1% of their respective fat/gland ratios from 10 to 200 keV. The density ranged from 0 percent glandular density to 100% glandular density in 6 steps. The inner clear acrylic section was not included in our comparison since acrylic is not a stable representation of tissue across a wide x-ray energy range. The M17 phantom was scanned 10 times on the DXA scanner without repositioning and the average %FAT value from each density step was found.

Cadaver Breasts: Four whole cadaver breast pair (eight breasts) were examined using both DXA and mammograms. The breasts were excised whole with all residual muscle tissue removed. Each breast was scanned by DXA twice without repositioning and once after flipping on the table 180 degrees to simulate repositioning due to a second visit. The breasts were positioned in as close to a craniocaudal view as could be constructed. The precision of the DXA scanner was defined by the variance (PROC GLM, SAS Institute, Cary, NC) of the breast tissue scans without repositioning. The precision associated with repositioning, an estimate of the expected in vivo precision for follow-up examinations, was defined using PROC GLM in the same way using the first scan and the last respositioned scan.



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For mammographic density, the cadaver breast films were acquired on a Sensorgraphe DMR (General Electric Medical Systems, Inc., Waukesha, Wisconsin) mammography machine. The films were read by a trained radiologist and the mammographically dense regions delineated on the film with a wax pencil. The films were digitized at 100  $\mu\text{m}$  resolution on a Lumisys 200 digitizer (Lumisys, Inc., Sunnyvale, CA). The mammographic density was then quantified by a research assistant on a workstation designed by the authors (16) by tracing the pencil lines with a cursor.

## Results

### Percent Glandular Density Calibration:

Percent Glandular Density as defined by the M17 phantom was compared to %FAT measured on the DXA scanner. Each step was analyzed using an 8.7  $\text{cm}^2$  regions of interest. Figure 2 is a plot of the reported percent glandular density (%GD) of the M17 phantom to the %FAT measured on the phantom for each phantom step. The relationship was found to be:

$$\%GD = -0.627 * \%FAT_{\text{DXA}} + 72.5 \quad \text{Equation 2.}$$

The slope of -0.627 shows a compression of the %GD range to that of %FAT such that 100 %FAT is 9.8 %GD and 0 %FAT is 72.5 %GD.

The cadaver breast characteristics are shown in Table 1. There was a wide range of values of Total Mass, Fat Mass, Lean Mass, and %FAT. The precision of the DXA scanner was characterized using the cadaver breast without repositioning. Table 2 is a summary of the DXA scanner precision results. The precision (standard deviation) is approximately 1 gram for a mean mass of 1 kg, or 0.1% CV. Using the above equation to convert %FAT to %GD, the %GD precision was 0.5% standard deviation on a mean value of 32%. The precision associated with

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repositioning results from the repositioned cadaver scans are shown in Table 3. The standard deviation on all values increases slightly. Thus, the overall precision is being limited by repositioning more so than x-ray measurements. The cadaver breast mammographic density, PD, and %GD were found to be correlated with an r-value adjusted for the sample size of  $r_{\text{adjusted}} = 0.83$ . However, because the number of samples was very low, the regression relation was highly influenced by each data point.

**Discussion**

We found that the percentage fat of breast tissue measured by DXA is highly correlated and linearly related to %GD on a standard mammographic phantom. In addition, PD was moderately to highly correlated with percentage glandular density measured by DXA.

It is of interest to note that %GD does not equal 1-%FAT. This is most likely since %FAT is measured relative to a two-compartment model of fat and muscle, not fat and glandular tissue. Even so, this relation should result in a slope difference between %FAT and %GD. The offset is most likely due to the QDR-4500A being calibrated to the in vivo 4-compartment model of body composition. This model uses underwater weighing to derive body density, which has a known offset to absolute standards of fat and lean tissue (17). We expect the in vivo precision to be similar to the cadaver precision with repositioning since flipping the breast 180 degrees would be a worst-case repositioning error.

There are other methods available to estimate body fat but only Dual X-ray Absorptiometry (DXA) (18), Computed Tomography (CT) (19) and Magnetic Resonance Imaging (MRI) (20) are capable of measuring the tissue composition of isolated body regions. Lee reported a 2% accuracy of segmenting breast fat from glandular/duct tissue in phantoms

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using whole breast MRI scanning. The slices were individually segmented into two compartments and all slices summed to get a total percent breast fat. In 40 women, the standard deviation of the group's mean value was 18% compared to 30% for mammographic density on the same women although the techniques were correlated  $r = 0.6$ . This suggests that mammographic density is related to segmented compositional density but with a variance that is influenced by non-density features. CT can provide a precise measure of tissue composition calibrated to electron density or absolute references. Kalef-Ezra described the normal breast electron density from CT volume scans on pre and postmenopausal women (19). However, the whole organ radiation dose of CT limits its usefulness as a screening tool. Neither technique, to the author's knowledge, has been used to quantify cancer risk based on breast density.

Dual energy mammographic imaging is not a new concept and has been demonstrated for selecting calcifications and improved image contrast (21-25). Breitenstein (26) and Shaw (27) reported on theoretical calculations of signal-to-noise ratios for single versus dual energy mammography to quantify tissue density using idealized phantoms. However, there is a significant effort necessary to generate precise and accurate quantitative DXA images on standard mammography equipment (i.e. filtering, poor dynamic range of film, availability of digital mammography units, x-ray tube stability). The wide spread use of digital detectors and the replacement of x-ray film should make DXA imaging more feasible on standard digital mammography machines.

Our study has several limitations. First there were only a small number of cadaver breasts available for our estimates of precision and the regression statistics. In addition, we used a conventional DXA device optimized for bone density and whole body composition measures. In contrast to tomographic images and more specialized scan modes possible on digital

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mammography machines, the DXA images acquired in this study have no diagnostic value beyond determining tissue density and mass. Lastly, choosing alternative DXA energies may improve the technique's tissue selectivity even further.

In conclusion, we have shown that conventional DXA devices can be calibrated to measure Percent Glandular Density. DXA can quantify breast density to approximately 1% precision limited principally by repositioning. The agreement between Mammographic Density, PD, and %GD is moderately to highly correlated. Thus, compositional densitometry may be more accurate and precise than mammographic density for quantifying breast cancer risk. However, it has not been demonstrated whether compositional breast density measured using any technique is more predictive or discriminating than mammographic density in determining breast cancer risk. In vivo studies to quantify %GD and cancer risk are warranted.

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**Figure 2: Plot of (1-%FAT) measured on the DXA device to %GD as reported on the phantom. Error bars are shown but do not extend beyond the dimension of the plot symbol.**

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**Table 1: Mass range and %FAT range of the whole breast**

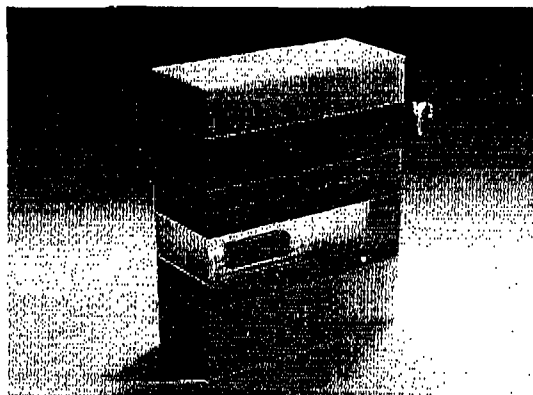
Fat Mass Range	149.1 - 1303.6 g
Lean Mass Range	141.8 - 371.4 g
Total Mass Range	554.6 - 1675 g
Percent Fat Range	13.8 - 82.5%

**Table 2: Precision of the DXA device without breast repositioning.**

Variable	Units	Mean	SD	CV (%)
Fat	grams	645.5	4.1	0.6
Lean	grams	263.2	3.7	1.4
Total Mass	grams	908.7	0.8	0.1
Percent Glandular Density	percent	32.0	0.5	

**Table 3: Precision of the DXA device with breast repositioning.**

Variable	Units	Mean	SD	CV (%)
Fat	grams	708.0	16.3	2.3
Lean	grams	263.0	8.0	3.0
Total Mass	grams	971.8	9.3	1.0
Percent Glandular Density	percent	30.9	1.1	



**Figure 1: Density step phantom (CIRS, Inc., Norfolk, VA) used to calibrate the DXA device to units of percent glandular density (%GD). Six step range in %glandular density from 0% (pure adipose fat) to 100% (pure breast glandular tissue).**

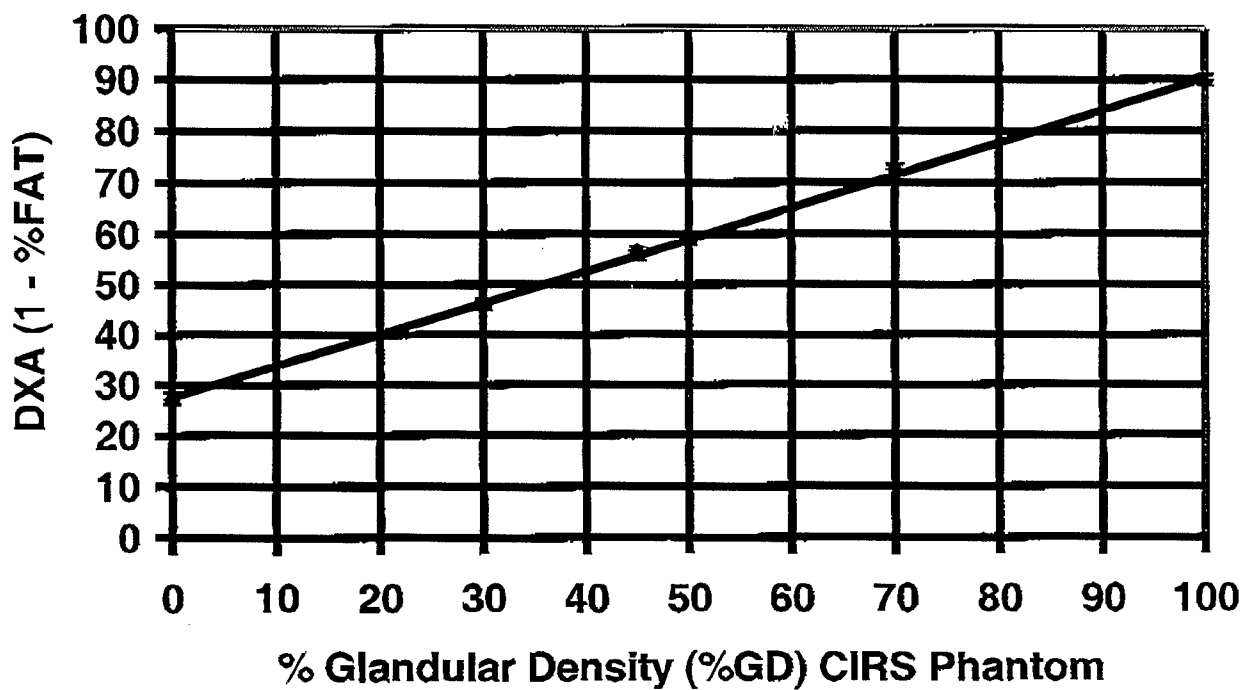


Figure 2: Plot of (1-%FAT) measured on the DXA device to %GD as reported on the phantom. Error bars are shown but do not extend beyond the dimension of the plot symbol.





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